REMARKS

This Amendment and Response is submitted in response to the Office Action mailed 27 February 2002. Claims 11, 14, 15, 19, 20, and 28-50 are pending in the application, claims 12, 13, 16-18, and 21-27having been cancelled by this amendment, and claims 28-50 having been added by this amendment. Claims 11-27 were finally rejected in the Office Action mailed 27 February 2002. Withdrawal of the rejection and reconsideration with an eye toward allowance is respectfully requested in view of the amendments and arguments detailed below. A marked-up version of paragraphs and claims amended as above is attached herein, entitled **Version with Markings to Show Changes Made**. For the Examiner's convenience, a clean copy of all pending claims is attached, entitled "**Appendix A: Pending Claims**". Support for the above claim amendments can be found throughout the originally filed specification, claims and drawings. For example, support for amendments to claim 11 can be found on page 94, line 16 - page 95, line 9. Support for new claims 28-35 can be found on pages 111-114.

Sequence Listing

The sequence listing filed on 23 January 2002 failed to comply with the requirements of 37 C.F.R. §1.825 due to a damaged disk. Applicants enclose herein a floppy disk containing the sequence listing in computer readable form. The computer readable sequence listing was prepared through use of the software program 'PatentIn' provided by the PTO. The information contained in the enclosed computer readable disk is identical to that of the paper copy which was filed by the Applicant on December 20, 2001 and contains no new matter. Applicants trust that the sequence listing now complies with 37 C.F.R. §1.825, and the objection will be withdrawn.

35 U.S.C. §112 Rejections

Claim 16 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that the term "higher harmonic analysis" in claim 16 is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicants respectfully disagree.

First, Applicants reiterate their position that the term 'higher harmonics' is well known in the art, specifically in the generalized field of signal processing. In general, a time-varying signal can be expressed as a sum of components, each having a different frequency. One of these components is generally the 'fundamental component', and the others 'harmonics'. Exciting a system with an input signal having a particular frequency, may yield a response at the input 'fundamental' frequency as well as other 'harmonic frequencies'. Components of the response at the harmonic frequencies are generally referred to as harmonics. Applicants draw the Examiner's attention to an introductory signal processing text, W.

M. Siebert "Circuits, Signals, and Systems," 1986 (a portion of which is attached herein as Exhibit A). On page 375, the terms 'fundamental' and 'harmonics' are described with reference to signal components. Indeed, the text identifies the classical nature of these terms as deriving from the relationship with musical consonances, and having been introduced by Sauveur in 1704. Other references may be readily provided should the Examiner require further objective evidence of the widespread acceptance of the term "harmonics", or "higher harmonics" in the art.

The Examiner further states that since the specification shows that the higher harmonic frequencies can range from second to tenth harmonics or greater (page 94), there is no standard for the higher harmonic signal. Applicant respectfully disagrees. On page 92 of the specification, Applicants clearly state the motivation for analyzing higher harmonic components. The background capacitance (or noise), responds linearly to AC signals, thereby producing very little signal at higher harmonic frequencies. In contrast, the desired signal (for example, ferrocene response) is non-linear. Therefore, at the higher harmonic frequencies, the signal-to-noise ratio is improved. One skilled in the art would readily appreciate that the choice of which harmonic frequency (2nd, 3rd, 4th, 5th, etc) to utilize is determined by identifying the harmonic frequency at which the signal strength and signal-to-noise ratio are such that the signal can be identified. Accordingly, Applicants request withdrawal of the 35 U.S.C. §112 rejection.

35 U.S.C. §102(e) Rejections

Claims 11 and 13 were rejected under 35 U.S.C. §102(e) as anticipated by, or, in the alternative, under 35 U.S.C. §103(a) as obvious over Megerle (U.S. Patent No. 5,874,046) in light of Meade (U.S. Patent No. 6,013,459). As a preliminary matter, Applicants respectfully note that a 35 U.S.C. §102 rejection over two references is generally improper.

Megerle is directed toward a sensor system where the electrical conductance through oligonucleic sequences affixed to electrodes is measured using voltammetry, pulse polarography, and/or impendence measurements (col. 6). Megerle discusses the signal intensity in col. 12. Specifically, Megerle notes that the signal intensity may become too low to detect in certain systems. Megerle discloses boosting the signal intensity for a relatively long target sequence by employing several oligonucleotides coded for different portions of the same target sequence.

In contrast, the present invention exploits the non-linearity of the assay complex response to achieve an improved signal-to-noise ratio in the harmonic components of the signal. Accordingly, claim 11 recites "applying an input waveform to said electrode to generate an output waveform comprising a harmonic component", "detecting said output waveform at said electrode", and "analyzing said harmonic component to determine the presence of said target analytes". Applicant notes that claim 13 has been amended to depend from, and include all limitations of, claim 11.

An anticipation rejection requires that a single reference expressly or inherently disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)). Additionally, the reference must enable and describe the claimed invention "sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." 31 USPQ2d at 1673. To be enabling, the reference must teach the skilled artisan how to make and use the full scope of the claimed invention without undue experimentation. *See Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997).

As discussed above, Megerle does not teach or disclose a method for improving signal intensity that involves "applying an input waveform to said electrode to generate an output waveform comprising a harmonic component" or "analyzing said harmonic component to determine the presence of said target analytes" as in claim 11, nor are these limitations inherently known in cyclic voltammetry. Therefore, Applicants respectfully request that the 35 U.S.C. §102(e) rejection of claims 11 and 13 over Megerle be withdrawn.

35 U.S.C. §103(a) Rejections

The Examiner indicated that claims 11 and 13 may be alternatively rejected under 35 U.S.C. §103(a) over Megerle in view of Meade.

Megerle is discussed above.

Meade is directed toward the detection of analytes, and discloses a variety of electronic techniques that may be utilized to interrogate an electrode comprising redox active molecules.

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g.*, *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. § 2142. To establish a *prima facie* case the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention. Furthermore, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. § 706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established. Applicants submit that neither reference, taken alone or in combination, teaches or suggests the use of harmonics.

Applicants submit that Meade fails to disclose advantageously leveraging the non-linearity of the assay complex response to improve the signal-to-noise ratio, as discussed above. Specifically, Meade does not teach or suggest "applying an input waveform to said electrode to generate an output waveform comprising a harmonic component" or "analyzing said harmonic component to determine the presence

of said target analytes" as in claim 11. Applicants submit, therefore that Megerle and Meade, taken alone or in combination, fail to disclose all limitations of Applicants' claim 11. Further, claim 13 is dependent from and contains all limitations of claim 11. Accordingly, Applicants respectfully request that the 35 U.S.C. §103(a) rejection of claims 11 and 13 over Megerle in view of Meade be withdrawn.

Claims 12, 19, 21, and 23-27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Megerle as applied to claims 11 and 13, and further in view of Meade and Giancoli. Applicants note that claims 12, 21, and 23-27 have been cancelled, obviating the rejection. However, in the interest of a complete response, Applicants demonstrate below that at least claim 11 is patentable over the combination of references.

Megerle and Meade are discussed above.

Giancoli is a physics text that discusses well known properties of AC signals.

Applicant submits that Giancoli clearly fails to disclose advantageously leveraging the non-linearity of the response to improve the signal-to-noise ratio, as discussed above. Specifically, Giancoli does not teach or suggest "applying an input waveform to said electrode to generate an output waveform comprising a harmonic component" or "analyzing said harmonic component to determine the presence of said target analytes" as in claim 11. Applicants submit, therefore that Megerle, Meade, and Giancoli, taken alone or in combination, fail to disclose all limitations of Applicants' claim 11.

Claims 12, 16, 21, and 22 were rejected under 35 U.S.C. §103(a) as being unpatentable over Megerle in light of Meade as applied to claims 11 and 13 above, and further in view of Singhal et al. Again, Applicants note that claims 12, 16, 21, and 22 have been cancelled, obviating the rejection. In the interest of a complete response, however, Applicants address Singhal below.

Megerle and Meade are discussed above.

Singhal discloses electrochemical detection of purine- and pyrimidine-based nucleotides with sinusoidal voltammetry. Singhal discloses analysing harmonic components of the output signal to identify the presence of nucleotides.

The Examiner states that it would have been obvious to simply replace one detection method (cyclic voltammetry) with another detection method (sinusoidal voltammetry) for the detection of nucleic acid hybridization.

Applicants reiterate that Singhal fail to teach or suggest analyzing a harmonic component of an output waveform to determine the presence of a target analyte where the target analyte is contained in an assay complex further comprising an electron transfer moiety (ETM), as in Applicants' claim 11. Singhal discloses instead the detection of nucleic acids that adsorb on a copper surface (see page 3554, col. 2, paragraph 3). The electroactive response is explained by the mechanism for the oxidation of sugars and amines on copper (page 3554, col. 2, paragraph 3, and page 3557, col.1, paragraph 2).

In contrast, Applicants recite a system comprising an assay complex comprising an electron transfer moiety (ETM). Applicants submit that Singhal fails to provide the motivation to use harmonic analysis and other electronic techniques for systems comprising an assay complex comprising an electron transfer moiety (ETM). Accordingly, Applicants submit that at least claim 11 is patentably distinct therefore over the combination of Megerle, Meade, and Singhal.

Claims 12 and 17 were rejected under 35 U.S.C. §103(a) as being unpatentable over Megerle in light of Meade as applied to claims 11 and 13 above, and further in view of Cheever et al. Further, claim 18 was rejected under 35 U.S.C. §103(a) as being unpatentable over Megerle in light of Meade and Cheever as applied to claims 11-13 and 17 above, and further in view of Wood et al. Applicants note that claims 12, 17, and 18 have been cancelled, obviating the rejection. In the interest of a complete response, however, Applicants discuss Cheever and Wood below.

Megerle and Meade are discussed above.

Cheever is directed toward the use of Fast Fourier Transforms (FFTs) to perform correlations on DNA sequences. More specifically, Cheever recites methods to save processing time when comparing DNA sequences.

Wood is directed toward the use of a joint time-frequency transform (JTFT) to analyze cardiac vibrations.

As with Megerle and Meade above, Applicants submit that Cheever and Wood fail to disclose exploiting the non-linearity of the assay complex response, as disclosed by Applicants and recited in claim 11. Applicants' claim 11 clearly recites "applying an input waveform to said electrode to generate an output waveform comprising a harmonic component" and "analyzing said harmonic component to determine the presence of said target analytes". Applicants submit that the combination of Megerle, Meade, and Cheever or Megerle, Meade, and Wood still fail to recite all limitations of Applicants claim 11.

Claims 20 and 22 were rejected under 35 U.S.C. §103(a) as being unpatentable over Megerle in light of Meade as applied to claims 11 and 13 above, and further in view of Nederlof et al. Applicants submit that claim 22 has been cancelled, obviating the rejection. However, in the interest of a complete response, Applicants discuss Nederlof below.

Nederlof is directed toward the detection of hybridization with fluorescence. Nederlof discloses the use of digital filters to improve the detection capabilities.

The Examiner states that it would have been obvious to use digital filtering to detect nucleic acid hybridization using image cytometry comprising a digital filter in view of Megerle in light of Meade and Nederlof, because the simple replacement of one electronic detection method (cyclic voltammetry) from another electronic detection method (image cytometry) in the detection of nucleic acid hybridization would have been prima facie obvious at the time the invention was made.

As with Megerle and Meade above, Applicants submit that Nederlof fails to disclose exploiting the non-linearity of the assay complex response, as disclosed by Applicants and recited in claim 11. Applicants claim 11 clearly recites "applying an input waveform to said electrode to generate an output waveform comprising a harmonic component" and "analyzing said harmonic component to determine the presence of said target analytes". While Nederlof does advantageously employ digital filtering, the reference is concerned with fluorescence, and image improvement, not the enhancement of an electrochemical signal generated by electron transfer through a nucleic acid. Applicants submit that the combination of Megerle, Meade, and Nederlfo still fail to recite all limitations of Applicants claim 11. Claim 20 depends from and includes all limitations of claim 11. Accordingly, Applicants request that the 35 U.S.C. §103(a) rejection of claim 20 be withdrawn.

New Claims

Applicant has added new claims 28-50 which further distinguish over the cited art. For example, Claim 28 further recites an electrode having an asymmetrical response to the input waveform. Claims 29 and 30 recite particular features of embodiments of the electron transfer moiety. Claims 31-34 recite additions to the sample including a co-reductant or co-oxidant. The cited art fails to disclose or suggest these features. Other of the added claims present other features that are neither disclosed nor suggested by the cited art.

CONCLUSION

Accordingly, Applicant submits that the claims are now in condition for allowance and an early notification of such is earnestly solicited. The Examiner is invited to telephone the undersigned attorney in the event that further issues are identified that would preclude allowance of the claims.

While Applicant believes that no further fees are due at this time, the Commissioner is authorized to charge any fees that may be due as a result of filing this amendment, including additional claims fees

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not already paid for, or other fees that have not been separately paid, to Deposit Account 06-1300 (Order No. A-65686-1/RFT/RMS/RMK).

Respectfully submitted,

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APPENDIX WITH MARKINGS SHOWING CHANGES MADE

Claims 12, 13, 16-18, and 21-27 were canceled.

Claims 11, 14, 15, 19, and 20 were amended as follows.

11. (Amended) A method of determining the presence of target analytes in a sample comprising:

a) applying said sample to ~~providing~~ an array comprising a plurality of electrodes, at least one of which comprises an assay complex comprising:

i) a capture binding ligand covalently attached to said electrode;

ii) a target analyte; and

iii) an electron transfer moiety;

b) applying an input waveform to said electrode to generate an output waveform comprising a harmonic component~~an electronic first input signal to said assay complex~~;

c) detecting said output waveform at said electrode; ~~an electronic output signal~~;

d) analyzing said harmonic component~~processing said detected output signal~~ to determine the presence of said target analytes.

14. (Amended) A method according to claim 11 ~~or 12~~ wherein said target analyte is a nucleic acid.

15. (Amended) A method according to claim 11 ~~or 12~~ wherein said target analyte is a protein.

19. (Amended) A method according to claim 11, ~~12 or 13~~ wherein said ~~processing~~ analyzing comprises the use of a peak recognition scheme.

20. (Amended) A method according to claim 11, ~~12 or 13~~ wherein said ~~processing~~ analyzing comprises a digital filter.

New claims 28-50 were added.

Appendix A: Pending Claims

11. (Amended) A method of determining the presence of target analytes in a sample comprising:

a) applying said sample to an array comprising a plurality of electrodes, at least one of which comprises an assay complex comprising:

i) a capture binding ligand covalently attached to said electrode;

ii) a target analyte; and

iii) an electron transfer moiety;

b) applying an input waveform to said electrode to generate an output waveform comprising a harmonic component;

c) detecting said output waveform at said electrode;

d) analyzing said harmonic component to determine the presence of said target analytes.

14. (Amended) A method according to claim 11 wherein said target analyte is a nucleic acid.

15. (Amended) A method according to claim 11 wherein said target analyte is a protein.

19. (Amended) A method according to claim 11, wherein said analyzing comprises the use of a peak recognition scheme.

20. (Amended) A method according to claim 11, wherein said analyzing comprises a digital filter.

28. (New) The method of claim 11, wherein said electrode has an asymmetrical response to said input waveform.

29. (New) The method of claim 28, wherein said electron transfer moiety is degradable.

30. (New) The method of claim 29, wherein said electron transfer moiety is luminol.

31. (New) The method of claim 28, further comprising adding a co-reductant to said sample.

32. (New) The method of claim 31, wherein said co-reductant is ferrocyanide.

33. (New) The method of claim 31, wherein said co-reductant has a lower redox potential than said electron transfer moiety.

34. (New) The method of claim 28, further comprising adding a co-oxidant to said sample.

35. (New) The method of claim 28, wherein said asymmetrical response is due to an enzyme-coupled reaction.

36. (New) The method of claim 11, wherein said input waveform is a voltage waveform and said output waveform is a current waveform, wherein said input waveform comprises an AC component having a first frequency and a first amplitude, and wherein said first amplitude is selected such that said output waveform comprises at least one non-linear harmonic component.

37. (New) The method of claim 11, wherein said harmonic component is chosen from the group consisting of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, and tenth harmonic components.

38. (New) The method of claim 11, wherein said method comprises analyzing a plurality of harmonic components of said output waveform.

39. (New) The method of claim 11, wherein said input waveform comprises a square wave.

40. (New) The method of claim 39, wherein said harmonic component is an even harmonic component.

41. (New) The method of claim 11, further comprising computing a fast fourier transform of said detected output waveform.

42. (New) The method of claim 11, further comprising computing a joint time-frequency transform of said detected output waveform.

43. (New) The method of claim 11, wherein said input waveform comprises a plurality of components, each having a different frequency.

44. (New) The method of claim 11, further comprising fitting said harmonic component to a first curve and a second curve, wherein said first curve describes a Faradaic signal and said second curve describes a background signal.

45. (New) The method of claim 44, wherein said first curve is based, at least in part, on a modified Gaussian distribution.

46. (New) The method of claim 44, wherein said second curve is a fifth order polynomial.

47. (New) The method of claim 44, wherein said fitting comprises minimizing a mean square error.

48. (New) The method of claim 46, wherein said fitting said fifth order polynomial comprises using singular value decomposition.

49. (New) The method of claim 11, wherein said analyzing comprises digital filtering.

50. (New) The method of claim 49, wherein said filtering utilizes a filter chosen from the group consisting of a match filter, a weiner filter, and a kalman filter.

Circuits, Signals, and Systems

The MIT Electrical Engineering and Computer Science Series

Harold Abelson and Gerald Jay Sussman with Julie Sussman,
Structure and Interpretation of Computer Programs, 1985

William McC. Siebert, *Circuits, Signals, and Systems*, 1986

Circuits, Signals, and Systems

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But perhaps the simplest and most useful form—and the one we shall employ almost exclusively in the sequel—is the *exponential form*:*

$$x(t) = \sum_{n=-\infty}^{\infty} X[n] e^{j2\pi nt/T} \tag{12.4–8}$$

$$X[n] = \frac{1}{T}\int_{-T/2}^{T/2} x(t) e^{-j2\pi nt/T}\, dt. \tag{12.4–9}$$

In the exponential form only a single integral is required to define the coefficients, but note that the sum in (12.4–8) extends over *negative* values of n (negative "frequencies"!) as well as positive values. However, if $x(t)$ is real (as we have previously tacitly assumed), then it follows at once from (12.4–9) that $X[-n]$ is the complex conjugate of $X[n]$:

$$X[-n] = X^*[n]. \tag{12.4–10}$$

Thus the complex amplitudes of the negative frequency components are entirely determined by those for positive frequencies. By comparison with previous results we can readily establish that, for $n \geq 0$,

$$\begin{aligned} a_0 &= X[0] & c_n &= 2|X[n]| \\ a_n &= 2\Re e[X[n]],\ n \neq 0 & \theta_n &= -\angle X[n] \\ b_n &= -2\Im m[X[n]] & X[n] &= \tfrac{1}{2}(a_n - jb_n) = \tfrac{1}{2}c_n e^{-j\theta_n}. \end{aligned} \tag{12.4–11}$$

The sine-cosine and magnitude-angle forms are rarely used for complex $x(t)$, but the exponential form (12.4–8) can easily be applied to complex waveforms (although, of course, (12.4–10) will not then be correct).

Example 12.4–1

For the square wave of Example 12.3–1 we have, from (12.4–9),

$$\begin{aligned} X[n] &= \frac{1}{T}\int_{-T/4}^{T/4} 1\, e^{-j2\pi nt/T}\, dt = \frac{1}{T}\left(\frac{T}{-j2\pi n}\right) e^{-j2\pi nt/T}\Big|_{-T/4}^{T/4} \\ &= \frac{1}{-j2\pi n}\left[e^{-j\pi n/2} - e^{j\pi n/2}\right] \\ &= \begin{cases} \dfrac{(-1)^{(n-1)/2}}{\pi n}, & n \text{ odd} \\ 0, & n \text{ even}, n \neq 0 \\ 1/2, & n = 0. \end{cases} \end{aligned}$$

From (12.4–11) these results are in agreement with those of Example 12.3–1.

▶ ▶ ▶

*As before, the square brackets in $X[n]$ indicate that the variable n takes on only integer values.

The set of Fourier coefficients $\{X[n]\}$ of (12.4–9) collectively constitute the *spectrum* of $x(t)$, and the process of determining them is called *spectral analysis.** In particular, $X[0]$ is the *average* or *d-c* (for "direct-current") value of $x(t)$, and $X[1]$ is usually called the complex amplitude of the *fundamental component.* The angular frequency of the fundamental component is the reciprocal of the *fundamental period*, T, which is the smallest nonzero number such that

$$x(t+T) = x(t). \tag{12.4–12}$$

For $n > 1$, $X[n]$ is often called the complex amplitude of the n^{th} *harmonic* of $x(t)$. The process of determining the set $\{X[n]\}$ is thus sometimes described as *harmonic analysis* of $x(t)$—the word "harmonic," of course, coming from the relationship with musical consonances.†

A periodic signal has a *discrete spectrum* because only a discrete set of frequencies is required in the spectral synthesis of such waveforms—the Fourier series (12.4–8). Discrete spectra are also called *line spectra*—an appropriate label since a convenient way to represent discrete spectral information graphically is in the form of a line or bar graph such as those shown in Figure 12.4–1. (Historically, the name "line spectrum" came from the fact that, in the usual display of the output of an optical spectrometer, a single isolated frequency component in the source appears as a bright line.) Since the Fourier coefficients are complex, two graphs—either real and imaginary parts, or magnitude and phase angle—are required for a complete representation.

For real waveforms, the conjugate symmetry of the coefficients implies that the real part and the magnitude of the spectrum are *even* functions of frequency or index n, whereas the imaginary part and phase angle are *odd* functions. Thus, if it is known that $x(t)$ is real, only the positive-frequency part of the spectrum need be shown. If, in addition to being real, $x(t)$ is an *even function*, that is, if $x(-t) = x(t)$, then it follows at once from (12.4–3) and (12.4–9) that the coefficients $X[n]$ are all *real* and that the sine-cosine form contains *cosines only.* Conversely, if $x(t)$ is real and *odd*, that is, if $x(-t) = -x(t)$, then the coefficients $X[n]$ are all purely *imaginary* and the sine-cosine form contains *sines only.*

*The word "spectrum" was introduced into physics by Newton (1664) to describe the analysis of light by a prism into its component colors or frequencies. The word is variously used in the mathematical and physical literature to denote the sets $\{X[n]\}$, $\{|X[n]|\} = \{c_n\}$, $\{|X[n]|^2\}$, etc. In this book "spectrum," without any modifying adjectives, will generally refer to the set of complex amplitudes $\{X[n]\}$; other types of spectra will be identified by labels such as "magnitude spectrum" or "power spectrum."

†That the idea of spectral analysis of sounds (in at least a limited sense) antedated Fourier is illustrated by the fact that Mersenne suggested in 1636 that a vibrating string "struck and sounded freely makes at least five sounds at the same time, the first of which is the natural sound of the string and serves as the foundation for the rest—[which] follow the ratio of the numbers 1, 2, 3, 4, 5." The terms "fundamental" and "harmonic" were introduced by Sauveur in 1704—more than 100 years before Fourier's prize paper. (For an interesting discussion of the early history of sound analysis, see R. Plomp, *Experiments on Tone Perception* (Soesterberg, Netherlands: Institute for Perception RVO-TNO, 1966).)